NOT FOR PEER REVIEW

KEY PAPER EVALUATION

Telcagepant is a new oral treatment for migraine

Evaluation of Ho TW, Ferrari MD, Rodick DW et al. Efficacy and tolerabilitiy of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. The Lancet 2008;372:2115-2123.

By Sheila A Doggrell PhD DSc

School of Life Sciences, Queensland University of Technology, GPO Box 2334, QLD4001, Australia

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Background: Migraine is a common cause of disability. Many subjects (30-40%) do not get a response to the 5-$HT_{1B/1D}$ agonists (the triptans) commonly used in the treatment of migraine attacks. Calcitonin Gene-Related Protein (CGRP) receptor antagonism is a new approach to the treatment of migraine attacks. *Objectives/methods:* This evaluation is of a Phase III clinical trial comparing telcagepant, an orally active CGRP receptor antagonist, with zolmitriptan in subjects during an attack of migraine. *Results:* Telcagepant 300 mg has a similar efficacy to zolmitriptan in relieving pain, phonophobia, photophobia and nausea. Telcagepant was better tolerated than zolmitriptan. *Conclusions:* The initial Phase III clinical trial results with telcagepant are promising, but several further clinical trials are needed to determine the place of telcagepant in the treatment of migraine attacks.

Keywords clinical trial, CGRP receptor antagonism, migraine attack, telcagepant, zolmitriptan

1. Introduction

Over 23 million people in the US suffer from migraine, and this migraine is a major cause of disability and work loss [1]. The present medicines of choice in the treatment of migraine attacks are the triptans, which are agonists at 5-$HT_{1B/1D}$ receptors in the central nervous system and on blood vessels. However, 30-40% of subjects with migraine do not respond to triptans, and those who have severe headache, presence of photophobia/phonophobia, and have nausea are more likely to be non-responders [2]. The other major problem with the triptans is that as 5-HT_{1B1D} receptors caused vasoconstriction, the triptans are contraindicated in subjects with cardiovascular disease. Thus, the search for more effective and safer drugs for the treatment of migraine attack continues.

Calcitonin Gene-Related Protein (CGRP) seems to have a pivotal role in migraine attacks. CGRP is present in the locations involved in migraine (e.g. trigeminal ganglion) [3]. In animal models of migraine attacks, CGRP is released [3]. In subjects with migraine, the levels of CGRP are raised during an attack and fall during recovery, and the infusion of CGRP causes headache similar to migraine [3]. This suggests that CGRP receptor antagonists may be useful in the treatment of migraine attacks. This evaluation briefly describes the proof-of-concept trial with the CGRP receptor antagonist BIBN 4096, and then the Phase II clinical trial with an orally active CGRP antagonist (telcagepant) during a migraine attack, and then describes (in more detail) the recently published Phase III clinical trial with telcagepant.

2. Proof-of-concept

Although BIBN 4096 (olcegepant) is a nonpeptide, selective and potent antagonist at CGRP receptors, it is not suitable for routine use in migraine, as it has to be given intravenously [4]. Nevertheless, BIBN 4096 was subjected to a clinical trial in migraine, to test the concept that CGRP receptor antagonism could be useful in the treatment of migraine. In this trial, when a migraine attack started, the subject had to report to a centre, where they (n = 126) were given placebo or a range of doses of BIBN 4096 (0.25-10 mg) intravenously [4]. The primary efficacy end point was a response, defined as the reduction of severe or moderate headache to mild or moderate headache [4]. This response was achieved in 27% of subjects with placebo, and there was a much greater response of between 60-80% with BINB

4096 2.5 mg, 5 mg and 10 mg [4]. None of the subjects given placebo experienced paresthesia ("pins and needles"), but 8% of subjects given BIBN 4096 did [4]. This trial provided proof-of-concept that CGRP receptor antagonism relieves migraine attacks.

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3. Phase II with telcagepant

Telcagepant is a potent, orally bioavailable CGRP receptor antagonist [5]. In a Phase II clinical trial, telcagepant was compared to rizatriptan 10 mg, and placebo, with the drugs being taken orally by the 225 outpatient subjects during an attack of migraine [6]. Pain relief at two hours, which is the reduction of moderate or severe pain to no or mild pain, occurred in 46% of subject taking placebo, and this was increased to 68% with telcagepant 300 mg and to 70% with rizatriptan 20 mg [6]. Sustained pain relief at 24 hours, was 24% in the placebo group, and 53% and 33% with telcagepant and rizatriptan, respectively [6]. Both telcagepant and rizatriptan were well tolerated, and there was no paraesthesia with telcagepant [6].

4. Phase III with telcagepant

The clinical trial showing that telcagepant is as effective as zolmitriptan in the treatment of acute migraine [7] is considered in this section.

4.1. Methods and results

The study involved 81 primary care or headache centres in the US and Europe. Subjects had to have had one to eight moderate or severe migraines attacks per month with or without aura in the two months prior to enrolment. As telcagepant is metabolised by CYP3A4, subjects taking potent inhibitors or inducers of this enzyme were not permitted to enrol. Subjects with a history or presence of cardiovascular disease or uncontrolled hypertension were excluded from the trial, as these conditions are a contraindication for zolmitriptan.

The 1380 subjects enrolled were predominantly women (~85%) and white (~95%), and had a mean age of ~42 years old. Only ~15% used migraine prophylaxis treatment, and more subjects used triptan treatment (~45%) than NSAID treatment (~25%) in an attack of migraine.

Subjects were randomised 1:1:1:1 to placebo, zolmitriptan 5 mg, telcagepant 150 mg or telcagepant 300 mg, and told to take their medication orally when they had a moderate or severe migraine attack. A second dose was permitted if the migraine was still occurring after 2 hours, or if it recurred in 48 hours. The second dose was a placebo for those that initially took placebo or zolmitriptan, whereas the second dose was a placebo or telcagepant for those who initially took telcagepant.

Headache severity was recorded on a 4-point scale (no pain, mild pain, moderate pain, and severe pain) at the time of taking the drug or placebo, and then every 30 minutes for 3 hours, followed by assessment after 4, 6, 8 and 24 hours. At the same time, functional disability was also rated on a 4-point scale (normal, mildly impaired, severely impaired, and requires bed rest). The presence of absence of nausea, vomiting, photophobia and phonophobia were also recorded.

The primary endpoints at 2 hours were pain freedom, pain relief, no phonophobia, no photophobia, and no nausea. Telcagepant was better than placebo in relieving an attack of migraine, assessed at each of the primary endpoints. Thus, two hours into the attack, telcagepant (150 mg and 300 mg) caused more subjects to be pain free, have pain relief, have no phonophobia or photophobia, and have no nausea than in the placebo group.

The secondary endpoints were 2-24 hour sustained pain freedom, total migraine freedom at 2 hours, and 2-24 hour total migraine freedom. Sustained pain freedom (2-24 hours) was also better with telcagepant than placebo. The higher dose of telcagepant (300 mg) gave higher odds ratios against placebo, suggesting a bigger effect, than the lower dose of telcagepant (150 mg) for all response parameters except nausea.

Telcagepant was also compared with zolmitriptan. Pain freedom at 2 hours occurred in 9.6% of placebo subjects, in 17.2% and 26.9% of telcagepant 150 and 300 mg subjects, respectively, and 31.3% of zolmitriptan subjects. Pain relief was also similar with telcagepant 300 mg (55.0%) and zolmitriptan (56.4%), as was the lack of phonophobia, photophobia and nausea at 2 hours. Total migraine freedom at 2 hours was 22.9% and 27.2% with telcagepant 300 mg and zolmitriptan, respectively. The time course for elimination of pain was similar with telcagepant 300 mg and zolmitriptan, which was faster than telcagepant 150 mg, which was in turn greater than with placebo.

Telcagepant was better tolerated than zolmitriptan. The overall incidence of adverse effects within 48 hours was lower with telcagepant 300 mg (34.1%) than with zolmitriptan (50.4%), and not much higher than with placebo (30.7%). Notably, there was less dizziness with telcagepant (5.1%) than zolmitriptan (11.0%), less fatigue (4.3% vs 7.0%), less paraesthesia (1.7% vvs 5.2%), and less chest discomfort (0.9% vs 2.9%). Tolerability was also measured over 14 days, but this did not differ greatly from the first 24 hours.

4.2 Discussion

The authors point out that their suggestion in the Phase II trial that telcagepant might be more effective than established treatment in providing sustained duration of pain relief or pain freedom up to 24 hours was not supported in this Phase III study. Telcagepant was well tolerated and this is an advantage over zolmitriptan.

Some subjects were excluded due to contraindications for zolmitriptan, and further studies are required to determine the safety and efficacy of telcagepant in subjects with cardiovascular disease.

5. Expert opinion

5.1 Onset of action

Telcagepant and zolmitriptan were taken orally in this Phase III comparison, and the effectiveness was measured at two hours. One of the most important parameters to measure when investigating medications for the treatment of a migraine attack is the onset of action. Obviously, subjects require relief from the pain of migraine as quickly as possible. Onset of action was not measured in the Phase III clinical trial comparing oral telcagepant and zolmitriptan, and this is an important omission. Future trials should determine the onset of action with telcagepant. Also, as sumatriptan and zolmitriptan are available as intranasal sprays that have higher pain free rates than oral preparations at 15 minutes after administration [8], oral telcagepant should be compared to these for both onset and duration of action. The manufactures (Merck Research Laboratories) should also consider whether telcagepant can be formulated for intranasal delivery.

5.2 Subjects taking medication which interact with zolmitriptan

In the Phase III study comparing telcagepant with zolmitriptan, subjects taking selective serotonin transporter inhibitors, dual noradrenaline and serotonin transporter inhibitors, and monamine oxidase inhibitors were not allowed to enrol, as these medicines interact with zolmitriptan, and other triptans, to cause serotonin toxicity. It would be of interest to test telcagepant in these subjects to determine whether it provides relief of migraine in those who cannot take the triptans.

5.3 Migraine that is unresponsive to the triptans

Only about 60% of subjects with migraine get a response at 2 hours with triptans (sumitriptan, zolmitriptan, naratriptan etc), and only about 20-30% of subjects are pain free at 2 hours [9]. It would be of interest to test telcagepant in subjects who are unresponsive to the triptans.

5.4 Combination therapy

The combination of sumitriptan and naproxen sodium was more effective than sumitriptan alone in migraine attacks [10]. Thus, more subjects on the combination were pain free at 2 hours (sumitriptan/naproxen, ~32%; sumitriptan, ~24%), and had headache relief at 2 hours (~70% vs ~61%) [10]. The combination of sumitriptan and naproxen sodium was also more effective than naproxen alone [10]. The incidence of adverse effects was similar with sumitriptan/naproxen and sumitriptan alone [10]. For telcagepant to be commonly used in the treatment of migraine attacks, it will need to be as effective and as well tolerated as the sumitriptan/naproxen combination. Thus, a clinical trial comparing telcagepant to sumitriptan/naproxen in migraine attacks is indicated. Alternatively, telcagepant in combination with naproxen could be compared to sumitriptan/naproxen in clinical trial of subjects with migraine

As telcagepant and zolmitriptan have different mechanisms of action this could lead to additive benefits, and they could be considered for combination in the treatment of migraine attacks. Thus, the combination of telcagepant and zolmitriptan could be compared to telcagepant and zolmitriptan monotherapy in subjects during a migraine attack.

5.5 Conclusions

As a CGRP receptor antagonist, telcagepant represents a new approach to the treatment of migraine attacks. In Phase III clinical trial, telcagepant has a similar efficacy to zolmitriptan, but has the advantage of being better tolerated. Several

further clinical trials are needed to determine the place of telcagepant in the treatment of migraine attacks.

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